Docket No. 55107 (71526) APPLICANT: S. Mori et al. SERIAL NO: 09/674,337

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REMARKS

I. Support for the Amendments

Claims 1-26 were originally in the application. Non-elected claims 8-26 were previously withdrawn. Claims 4, 5, and 7 were canceled during previous Amendments.

Claims 1-3 and 6 were in the application. Claims 1 and 3 have been amended, claims 2 and 6 have been canceled without prejudice, and new claims 27-36 have been added. No new matter has been added by virtue of these amendments. Claims 1, 3, and 27-36 are presently in the application.

Support for amended claims 1 and 3 and for new claims 27-36 can be found in the original specification, figures, and claims. Claim 3, which was previously dependent on claim 1 is now dependent on claim 27. The language of new claims 33 and 34 reflects the language of canceled claims 2 and 6. Additional support for amended claims 1 and 3 and for new claims 27-36 can be found, e.g., from page 10, line 12, to page 11, line 5; from page 17, line 24, to page 18, line 8; in Figures 6 and 7; and in the Examples. Additional support for amended claim 1 and for new claims 27-31, 35 and 36 can be found, e.g., on page 3, second full paragraph; from page 10, line 12, to page 11, line 5; from page 17, line 24, to page 18, line 8; in Figures 6 and 7 and in the Examples. Additional support for new claims 27-36 can be found, e.g., on pages 6-7, carryover paragraph; on page 7, second full paragraph; on page 14, second full paragraph; on page 15, second full paragraph; and in the Examples, particularly in Examples 2 and 3.

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II. Status of the Claims

Claims 1-26 were originally in the application. Claims 1-26 were subject to an election/restriction requirement, and claims 1-7 were elected. Claims 8-26 were withdrawn without prejudice or disclaimer of any subject matter. Claims 2, 4, and 5-7 have been canceled, and new claims 27-36 have been added. Claims 1, 3, and 27-36 are presently in the application.

III. Nucleotide and/or Amino Acid Sequence Disclosures

The Examiner has noted that the paper copy and computer readable form (CRF) of the Sequence Listing filed with the previous amendment have been received and processed. Applicants thank the Examiner for notifying them of the status of the Sequence Listing.

IV. The Telephonic Interview

In view of the limited nature of the remaining rejection, Applicants respectfully requested a telephonic interview with the Examiner. Applicants wish to express their gratitude for the Examiner's willingness to grant a telephonic interview notwithstanding the finality of the present rejection, and Applicants thank the Examiner accordingly for extending this courtesy.

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IV. Rejection of Claims 1-3 and 6 under 35 U.S.C. §112, First Paragraph is Traversed in Part and Rendered Moot in Part

The Examiner has rejected claims 1-3 and 6 under 35 U.S.C. §112, first paragraph, for reasons relating to enablement. Applicants respectfully traverse the rejection.

First, Applicants respectfully submit that the amendments to claim 1 render the rejection moot. The Office Action states:

Claims 1-3 and 6 stand rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an isolated nicotianamine synthase comprising an amino acid sequence of SEQ ID NO: 1; does not reasonably provide enablement for a nicotianamine synthase having 50% identity to SEQ ID NO: 1 and comprising at least one of amino acid sequences (1)-(6). [P. 2, par. 4.]

Claim 1 has been amended to read:

1. (currently amended) An isolated or purified enzyme exhibiting nicotianamine synthase activity, wherein the enzyme comprises the polypeptide having an amino acid sequence of SEQ ID NO: 1.

The language of claim 1, as amended, falls within the parameters of the remarks in the Office Action. Claims 2 and 6, which were dependent on claim 1, have been canceled without prejudice. Applicants respectfully submit, therefore, that the rejection is rendered moot with respect to claims 1, 2, and 6.

In addition to the statement above, the Patent Office alleges:

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The standard for meeting the enablement requirement is whether one of skill in the art can make the invention without undue experimentation. The amount of experimentation to make the claimed nicotianamine synthase having more than 50% identity to SEQ ID NO: 1 and-comprising 101 conserved amino acid residues as recited in claim 1 is undue. SEQ ID NO: 1 is disclosed by the specification as an amino acid sequence of 328 amino acid residues. The claims require at least 50% of SEQ ID NO: 1 to be altered, where at least 164 amino acid residues are changed (deletion, insertion, substitution, or combinations thereof) in SEQ ID NO: 1, and of those 164 amino acid residues that are to be changed, 101 amino acids must be conserved as recited in claim 1. However, there remains 63 amino acid residues that are to be altered.

One of ordinary skill in the art would have to screen and search for proteins having the changes in the amino acid sequence and then determine by enzymatic assays whether the protein has nicotianamine synthase activity. Such screening and searching is outside the scope of routine experimentation. Teaching regarding searching or screening for the claimed invention is not teaching for making the claimed nicotianamine synthase. Limiting the claims to recite the specific amino acid sequences of (1)-(6) does not overcome the rejection since no more than 32 amino acid residues out of a total of 328 amino acid residues of SEQ ID NO: 1 are accounted for.

The Examiner finds that one skilled in the art would require additional guidance, such as information regarding the specific 63 amino acid residues which can be changed without inactivating enzyme activity. Without such a guidance, the amount of experimentation left to those skilled in the art to make the invention is undue and well outside of routine experimentation. [Pp. 4-5, par. 4.]

Applicants respectfully disagree. Claim 3, as amended, is dependent on new claim 27. As noted previously, the claim language of claim 27, similar to the previous language of claim 1, does not require 50% of the residues to be non-identical, rather it is simply drawn to "a polypeptide having more than 50% identity," which could include, for example, polypeptides of 51% identity, 65% identity, 90% identity, and 99% identity. Moreover, new claim 27 requires the polypeptide to have a nicotianamine synthase activity of more than 25% of an equivalent amount of the nicotianamine synthase activity of the enzyme of SEQ ID NO:1. In essence, there is not only a sequence identity requirement, but also an activity requirement.

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While it has been alleged that this language would require undue experimentation, this argument seems to be related primarily to artificial derivatives of nicotianamine synthase, which have been obtained by mutation, such as site-directed mutagenesis. These days, if an isolated DNA encoding an enzyme derived from one specimen and a suitable expression system which can produce the functional enzyme are provided, barring unusual factors, it is not necessarily undue experimentation for one of skill in the art to isolate a DNA encoding a homologous protein from another species or another family member from the same species by using standard genetic engineering techniques, such as PCR or hybridization, and then producing the homologous protein by using the isolated DNA in the expression system. An appropriate enzyme activity assay can then be used to confirm the identification of the expressed protein. In those situations where the sequence is isolated and/or purified from a natural source, one of skill in the art need not be taught in advance which amino acid residue(s) can be changed without inactivating enzyme activity.

Moreover, Applicants respectfully submit that they have already obtained a number of sequences and that the conserved sequences and individual residues are supported by Figure 7. The specification as originally filed clearly discloses several naturally occurring enzymes derived from barley.

For the Examiner's convenience, Applicants have provided herewith a figure showing an amino acid alignment of nicotianamine synthases and identity (%) of included sequences thereof compared with HvNAS1 (SEQ ID NO:1; 100%). Applicants wish to note that the percentages of sequence identity for other barley sequences (SEQ ID NO: 3, 5, 7, 9, and 11) are 61% to 73%, while that of one non-barley sequence of the present invention (rice OsNAS1, SEQ ID NO: 15) is 75%.

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New claim 27 now includes an assay for measuring activity. It has been suggested that 90-95% identity might be more reasonable, but it is possible that other sequences may be less than 90-95% identical, but still have activity. Applicants also wish to note that this particular application was primarily focused on a protein, which, in an endogenous setting, is found, not in all organisms, but in certain types of plants, and which has an activity that is upregulated in an iron-deficient environment. Limiting the claims to enzymes isolated or purified from plants, however, would not cover artificial sequences. Applicants respectfully request the Examiner to reconsider these points.

As amended, claim 3 is dependent on claim 27, which recites a polypeptide having more than 50% identity with SEQ ID NO: 1 and one of six consensus sequence (see Figure 7), in addition to having more than 25% of the nicotianamine synthase activity of an equivalent amount of the nicotianamine synthase activity of the enzyme of SEQ ID NO:1. Figure 7 shows predicted amino acid sequences from seven cDNAs isolated from barley with the conserved amino acid sequences listed below. Therefore, one of ordinary skill in the art would recognize the potential importance of these conserved amino acids, relative to the variable amino acids, with respect to the claimed nicotianamine synthase. In addition, many of the non-conserved amino acid sequences have conservative changes. Moreover, the language of claim 27 also provides that the sequence must have more than 25% of the nicotianamine synthase activity of an equivalent amount of the nicotianamine synthase activity of the enzyme of SEQ ID NO:1. (See, e.g., page 7, second full paragraph; page 14, second full paragraph; page 15, second full paragraph; and the Examples, particularly in Examples 2 and 3.) The language of claim 27, therefore, provides both sequence parameters and activity parameters. (See, e.g., Regents of the University of California v. Eli Lilly & Co., 119 F.3d 1559, 43 U.S.P.Q.2d 1398 (Fed. Cir. 1997).) As a result, use of part or all of the consensus sequence(s) in the present invention would not require undue

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experimentation on the part of one of ordinary skill in the pertinent art.

Applicants respectfully disagree for the reasons outlined *supra*, but have amended claim 3 to read on new claim 27 in the interests of furthering the prosecution of the case. Applicants respectfully submit that the amendments place claims 1 and 3 in condition for allowance.

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CONCLUSION

In view of the foregoing amendments and remarks, the present application is respectfully considered in condition for allowance. An early reconsideration and notice of allowance are earnestly solicited.

It is believed that all outstanding rejections have been addressed by this submission and that all the claims are in condition for allowance. If discussion of any amendment or remark made herein would advance this important case to allowance, the Examiner is invited to call the undersigned as soon as convenient.

Applicants hereby request a two-month extension of time for the Amendment and accompanying materials. If, however, a petition for an additional extension of time is required, then the Examiner is requested to treat this as a conditional petition for an extension of time and the Commissioner is hereby authorized to charge our deposit account no. 04-1105 for the appropriate fee. Although it is not believed that any additional fee (in addition to the fee concurrently submitted) is required to consider this submission, the Commissioner is hereby authorized to charge our deposit account no. 04-1105 should any fee be deemed necessary.

Respectfully submitted,

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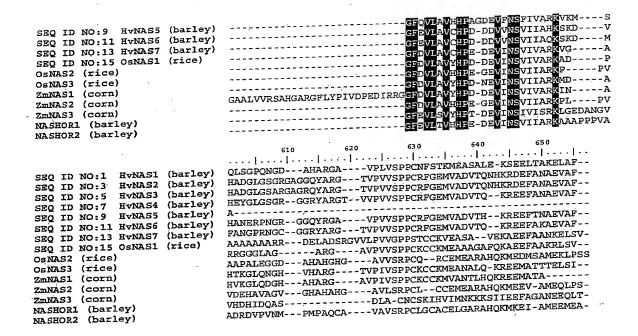
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ZmNAS2 (corn)
ZmNAS3 (corn)
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NASHOR2 (barley)
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SEQ ID NO:1
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NASHOR1 (barley)
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SEQ ID NO:5 HvNAS3 (barley)
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SEQ ID NO:11 HvNAS6 (barley)
                      SEQ ID NO:13 HvNAS7 (barley)
SEQ ID NO:15 OsNAS1 (rice)
OsNAS2 (rice)
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